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Vitrified-warmed single-embryo transfers may be associated with increased maternal complications compared with fresh single-embryo transfers

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KEY MESSAGE
Vitrified-warmed single blastocyte transfer may be associated with elevated miscarriage rate and increased risk of maternal complications such as pre-eclampsia and gestational diabetes mellitus, as well as neonatal complications such as large for gestational age neonates.

A B S T R A C T

Cryopreservation of embryos allows single-embryo transfer and storage of supernumerary embryos, maximizing cumulative pregnancy rates. The purpose of this retrospective cohort study was to compare pregnancy outcome in singletons born after fresh or vitrified-warmed single blastocyst transfer (SBT). Singleton live births resulting from SBT of fresh or vitrified-warmed embryos were compared. Primary outcomes were perinatal outcomes including small for gestational age (SGA), low birthweight, preterm deliveries (PTD), large for gestational age (LGA) and congenital malformations. Maternal complications included pre-eclampsia, placenta previa, placental abruption, gestational diabetes mellitus (GDM) and chorioamnionitis. Adjustment for confounding factors was performed. Of 1886 fresh SBTs and 1200 vitrified-warmed SBTs during the study period, vitrified-warmed SBTs compared with fresh SBTs resulted in significantly lower clinical pregnancy rate ($P < 0.0001$). Live birth and miscarriage rates calculated only for pregnancy with known outcome revealed lower live birth rates and higher miscarriage rates for the vitrified-warmed group. Perinatal complications were calculated for clinical pregnancies with known outcomes (12.9% catchment failure was excluded from analysis). The vitrified-warmed group showed a trend toward higher rates of pre-eclampsia, GDM, Caesarean delivery and LGA neonates. Rates of PTD and SGA were comparable. In conclusion, vitrified-warmed SBT might be associated with increased feto-maternal complications.

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Introduction

With the advancement of vitrification technology, there has been an increase in the practice of cryopreserved embryo transfer (ET). In addition, the pregnancy rates in cryopreserved ET cycles have improved steadily during the last decade, resulting in comparable or even higher implantation rates than in those with fresh cycles (Evans et al., 2014; Roque et al., 2013; Wong et al., 2014). Yet, fresh ETs are still the first choice in most assisted reproductive technology clinics. According to the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS), there were 86,340 fresh ET cycles and 40,015 cryopreserved ET cycles performed in the USA in 2013. Due to the elevated oestrogen and progesterone levels associated with ovarian stimulation, which may have a negative effect on the oocyte, endometrium and implanted embryo, a few authors have advocated the 'freeze all' policy, converting all cycles to frozen ET cycles (Santos et al., 2010; Shapiro et al., 2014; Weinerman and Mainigi, 2014).

The increased risk of pregnancy complications associated with IVF has mostly been attributed to the increased prevalence of multiple gestations associated with multiple ETs (Gjerris et al., 2009; Pinborg et al., 2005). However, recent reviews and meta-analysis have shown that singletons conceived by IVF are prone to higher rates of adverse pregnancy outcomes including low birthweight (LBW), preterm deliveries (PTL) and congenital malformation compared with spontaneously conceived singletons (Hansen et al., 2013; Henningsen et al., 2011; Schieve et al., 2002; Wang et al., 2005). Whether this adverse outcome is related to the IVF treatment or to the underlying subfertility itself is unclear (Jaques et al., 2010; Stern et al., 2015; Zhu et al., 2006).

Results of studies on adverse perinatal outcome in children born after frozen-thawed ETs have been mixed (Pelkonen et al., 2010, 2014; Pinborg et al., 2014; Wennerholm et al., 2013). Several studies found that cryopreserved ET cycle pregnancies resulted in a higher incidence of large for gestational age (LGA) infants, whereas fresh cycles were associated with a higher incidence of small for gestational age (SGA) infants (Pinborg et al., 2014). It is important to note that most studies comparing perinatal outcome of singleton births conceived after fresh and cryopreserved ETs included both single and multiple ETs. Therefore, part of the adverse perinatal outcome may be attributed to the vanishing twin phenomenon, which occurs in up to 10% of multiple ETs resulting in a singleton live birth (Evron et al., 2015). Our practice of single-embryo transfer (SET) was facilitated by the change in the Quebec policy for public IVF funding in August 2010. Accordingly, SET has been the standard of care and only in exceptional cases can more than one embryo be transferred.

In an attempt to decrease the incidence of multiple pregnancy related to assisted reproductive technologies, SET has been advocated (Luke et al., 2015; Practice Committee of American Society for Reproductive Medicine and Practice Committee of Society for Assisted Reproductive Technology, 2013) where excess supernumerary embryos are cryopreserved. This has resulted in an increasing rate of cryopreserved ET cycles.

The purpose of our study was to compare obstetric and perinatal outcomes of singletons resulting from a single fresh blastocyst transfer or a single vitrified-warmed blastocyst transfer.

Materials and methods

This was a retrospective cohort study evaluating SBT performed at the Reproductive Unit of McGill University Health Centre (MUHC) in Montreal, QC, Canada. We included all patients who underwent IVF treatment between December 2008 (the installation of our computerized fertility database system) and December 2012. The Research and Ethics Board of MUHC approved the study (MUHC study code 12–283-SDR).

We compared singleton live births resulting from transfer of a single fresh blastocyst (day 5 after oocyte retrieval) and those from a single vitrified-warmed blastocyst (day 5–6 embryos) transfer. Pregnancies achieved after transfer of more than one blastocyst or in which cleavage stage embryos were transferred were excluded from the study. We excluded six monozygotic twin (MZ) pregnancies resulting from a fresh blastocyst ET and two MZ twins from the transfer of a vitrified-warmed blastocyst transfer.

Our reproductive centre, one of the largest in the province of Quebec, provides fertility treatment to couples living in Montreal and the surrounding areas. Once a clinical pregnancy is established, patients are referred to their obstetricians, mostly outside our institution. Accordingly, data about the pregnancy outcome are not always available, even after meticulous efforts to contact patients. Those pregnancies were only included in analysing the clinical pregnancy rate. Analysis of maternal and perinatal complications was based only on clinical pregnancies with known outcome.

Controlled ovarian stimulation, oocyte retrieval, endometrial preparation and ET were performed according to our standard protocols. Women in the fresh SBT group underwent long or short gonadotrophin-releasing hormone (GnRH) agonist protocols or GnRH antagonist protocols. In the GnRH agonist protocol, all patients were treated with oral contraception for about 21 days (Marvelon®, MSD, Kirkland, QC, Canada) prior to starting the down-regulation with GnRH agonist (buserelin acetate, Sanofi-Aventis Inc., Laval, QC). In the long protocol, ovarian stimulation with gonadotrophins [one of the following: Gonal-F (EMD Serono Canada, Mississauga, ON), Repronex (Ferring Canada, North York, ON) or Puregon (Merck Canada Inc., Pointe-Claire, QC)] was started after achieving pituitary suppression. In the short protocol, ovarian stimulation was started 2 days after commencement of the GnRH agonist. Women who underwent the antagonist protocol started ovarian stimulation with gonadotrophins on cycle day 2–3 and GnRH antagonist was added 6 days after stimulation day (fixed protocol). Women were triggered with 10,000 units of human chorionic gonadotrophin (HCG) (Pharmaceutical Partners of Canada Inc., Richmond Hill, ON) after achieving at least three follicles ≥17 mm. Oocyte collection was performed 36 h later. Fertilization was achieved either by standard IVF or intracytoplasmic sperm injection (ICSI) according to the sperm parameters. All embryo cultures were performed under low-oxygen conditions (5% oxygen, 6% carbon dioxide, 89% nitrogen). All embryos were graded according to Gardner's blastocyst scoring criteria (Gardner et al., 2000, 2004). ET was performed under ultrasound guidance.

The luteal support protocol included Estrace 6 mg (Shire Canada Inc., St. Laurent, QC) and progesterone supplementation with either vaginal Endometrin 100 mg twice daily (Ferring Pharmaceuticals, Toronto, ON) or Crinone gel 8% once daily (EMD Serono, Mississauga, ON) up to 12 weeks of pregnancy.

Our clinic policy was that in the event of supernumerary embryos, only excess blastocysts of 3BB or higher were vitrified. Vitrification and warming of blastocysts was performed using an unmodified Cryotop method, as described by Kuwayama et al. (2005) and Zhu et al. (2011). It has been the only technique used for embryo cryopreservation at our laboratory since 2005. Blastocysts are taken through an equilibration step and a vitrification step at room temperature before being

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